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FROM THE ALLERGY DIVISION OF THE JEWISH HOSPITAL OF BROOKLYN

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ASTHMA AND HAY FEVER

Bronchial Asthma Due to Food Allergy Alone in Ninety-Five Patients. Rowe, A. H., Rowe, A., Jr., and Young, E. J.: J. A. M. A. **169**: 1158, 1959.

The case histories of 45 adults and 50 children in whom food allergy was the only cause of asthma were analyzed. Asthmatic attacks resulting from food allergy usually began before the third year and recurred every two to six weeks, with a remission during the summer. The attacks often started with nasal symptoms simulating an upper respiratory infection and were associated with fever, vomiting, and anorexia.

When food allergy was suspected, patients were put on trial diets. The cereal-free diet was the most effective one, but milk, egg, chocolate, and fish as well as other less common allergenic foods often had to be eliminated. By this method, 50 children were found to respond to dietary measures alone. About 52 per cent of these children had positive skin reactions to foods. Only 20 per cent of 30 adults ranging in age from 15 to 55 years showed positive skin reactions to foods. Among 15 patients past the age of 55, 33 per cent had positive skin reactions to foods.

The authors emphasize the importance of food allergy and stress the value of various elimination diets in the treatment of bronchial asthma. The diets often can be liberalized during the summer or after prolonged avoidance of a food when tolerance has developed. D. G.

Treatment of Pulmonary Emphysema. Bedell, G. N., and Seebohm, P. M.: J. A. M. A. **169**: 1699, 1959.

The authors distinguish between localized emphysema, most often a congenital anomaly, and generalized emphysema, which may be of undetermined cause or result from bronchial asthma, bronchiectasis, tuberculosis, silicosis, and other lung diseases. Patients with bronchial asthma and secondary emphysema experience paroxysmal dyspnea, usually nocturnal, and respond well to epinephrine and steroids, while patients with emphysema from other causes manifest dyspnea initially only on exertion, and their response to epinephrine and steroids is poor. Chest roentgenograms and pulmonary function tests are similar in both groups.

The treatment of emphysema itself consists of the use of the proper antibiotics following sputum and blood culture; when no organism can be found on culture, an intensive course of penicillin or erythromycin is indicated. The patient's activities should be commensurate with the vital capacity. Potassium iodide and bronchodilators, such as epinephrine and ephedrine, either as aerosols or systemically should be administered. Drugs depressing the cough center should be avoided. Sedation, if required, can be accomplished with phenobarbital or chloral hydrate. Oxygen should be reserved for advanced cases and for bouts of respiratory infection with aggravated hypoxia. Its administration should be limited to 20 to 30 minutes each hour to avoid the danger of carbon dioxide narcosis. Breathing exercises have theoretical value but do not enjoy patient acceptance. Intermittent positive pressure breathing and pneumoperitoneum have likewise been disappointing. In an occasional case of advanced emphysema with respiratory acidosis due to hypoventilation, artificial ventilation with a respirator often proves useful. Smoking should be discouraged.

The authors believe that it is most important to differentiate primary emphysema from the various secondary types and to treat the etiology if one can be found. Where this is not possible, treatment with antibiotics, iodides, and bronchodilators is the only choice. D. G.

Treatment of Hay Fever With Intranasal Hydrocortisone Acetate Powder. Taub, S. J., and Hecht, R. A.: Am. Pract. **10**: 469, 1959.

Hydrocortisone acetate, administered intranasally by means of an insufflator, was effective in the treatment of a group of patients suffering from grass and ragweed hay fever.

The patients were divided into two groups: new untreated patients and old patients who were not controlled by hyposensitization therapy. Of the total of 45 patients comprising both groups, results were excellent in 26, good in 12, fair in 3, and poor in 4. The average dosage was 2 to 3 puffs in each nostril 3 or 4 times a day. This was computed to be the equivalent of 5 to 15 mg. of hydrocortisone acetate per day. H. F.

Hydrocortisone Hemisuccinate by Inhalation in Children With Asthma. Smith, J. M.: Lancet **2**: 1248, 1958.

Fifty-seven asthmatic children were furnished with either a placebo mixture or a solution containing hydrocortisone to be taken daily by inhalation for relief of asthma. Both solutions were supplied in bottles containing droppers, calibrated to deliver approximately 5 mg. of hydrocortisone for each daily dose. Neither the patient nor the doctor was aware of the identity of the solution used for therapy. The same amount of solution was inhaled daily for one month, and the effectiveness of the treatment was judged by a daily symptom record kept by the mother of each child and also by a weekly computation of the volume of expired air in the first 0.75 second of a fast expiration. The subjective and objective results of a month's trial therapy disclosed that 14 per cent appeared to be benefitted by the placebo and 21 per cent by the hydrocortisone inhalation. These findings were not regarded as being statistically significant. The importance of conducting carefully controlled studies in order to evaluate properly different methods of therapy for asthmatic patients is stressed. R. W.

The "Climate Group" of Respiratory Allergy Patients: A Basic Climate Pattern With House Dust Sensitization as a Universal Principle in the Etiology. Ordman, D.: Arch. Internat. Allergy & Appl. Immunol. **12**: 162, 1958.

Experience of sufferers from perennial respiratory allergy in the Union of South Africa disclosed a "climate group" in whom symptoms were aggravated in the coastal regions but ameliorated inland. These patients were highly sensitive to coastal house dust which proved to be allergenically more potent than that from inland sources. No other etiological factor could be demonstrated. The pertinent literature which was reviewed indicated that similar "climate groups" exist in many other countries. Meteorologic data in different countries were analyzed. The coastal regions were characterized by constant high temperature and high relative humidity, both within narrow range, in contrast to the inland pattern which was characterized by a wide range of temperature and relative humidity throughout the day and during the year. I. G.

DERMATOLOGY

Hemorrhagic Skin Manifestations Following the Use of Prednisone and Prednisolone. Dordick, J. R., Sussman, L. N., and Bernstein, Z. L.: New York J. Med. **58**: 4019, 1958.

Steroids were given to 21 female and 9 male patients with rheumatoid disorders for periods ranging from 7 days up to 35 months. Of this group,

23 per cent developed some type of hemorrhagic skin manifestation (in the form of petechiae, purpura, ecchymosis, or easy bruising after mild trauma). None of the patients had positive hereditary backgrounds of hemorrhagic disease. Prior to starting treatment one patient had observed purpura following hydrocortisone therapy, and another developed thrombocytopenic purpura secondary to gold therapy for rheumatoid arthritis. The latter patient was kept on 10 to 20 mg. of prednisone for 16 months without developing any bleeding tendency. Salicylates were discontinued in all patients prior to starting steroid therapy. The only abnormal laboratory finding was a positive tourniquet test which remained positive in some patients for many weeks after the lesions had cleared and the hormone had been discontinued. The bleeding manifestations quickly terminated when the dosage of steroid was either stopped or lowered or when 100 mg. of ascorbic acid was given twice daily concomitant with the hormone therapy. Prednisone and prednisolone produced hemorrhagic lesions more frequently than cortisone, hydrocortisone, or corticotropin, but vitamin C apparently corrected the defect in intercellular cement substance caused by steroid therapy. R. W.

Chronic Penicillin Urticaria From Dairy Products Proved by Penicillinase Cures. Zimmerman, M. C.: Arch. Dermat. **79**: 1, 1959.

Four patients with chronic urticaria caused by penicillin sensitivity were injected with 800,000 units of penicillinase (Neutropen). In each instance the lesions disappeared. This effect was maintained for at least 6 to 8 days in those persons whose only penicillin exposure was assumed to be from dairy products. When dairy products were eliminated and no further exposure to penicillin therapy occurred, a single injection of 800,000 units of penicillinase was sufficient to produce a complete remission of the allergic reaction within 48 hours. When dairy products were not eliminated following the injection of penicillinase, the allergic reaction persisted. These data indicated that chronic urticaria due to penicillin was potentiated by small amounts of the antibiotic present as a contaminant in milk. Penicillinase was effective as both a diagnostic and a therapeutic tool in this study. R. W.

Prednisolone (Meti-Derm) as an Aerosol for Dermatoses. Robinson, H. M.: Arch. Dermat. **79**: 103, 1959.

A topical aerosol containing 50 mg. of prednisolone dissolved in isopropyl myristate and Freon was used in 79 patients with various types of eczematoid dermatitis. Patients were instructed to use a three-second spray which was held one or two inches away from the affected part of the body. Good results were attained in 82 per cent of the group, more than one-half of whom obtained complete healing of their lesions within 1 week of therapy. Bilateral paired comparisons were made on similarly involved regions in 12 patients using the prednisolone aerosol and a placebo spray. The prednisolone aerosol proved to be a much more effective agent than the control. The aerosol was especially useful in treating inflammatory lesions, large surface areas, and regions of the body which contained large amounts of hair. It was more effective in relieving pruritus than either creams or ointments to which steroids had been added. No side effects were observed. R. W.

Athrombocytopenic Purpura Caused by Chlorothiazide. Horowitz, H. I., Shapiro, B., and Rubin, I. L.: New York J. Med. **59**: 1117, 1959.

A 58-year-old housewife with rheumatic heart disease was hospitalized twice within a period of 14 months because of a rash on her hands and legs

of 9 days' duration. She was treated with chlorothiazide (Diuril), Digoxin, and a low-salt diet. Three days following her last dose of chlorothiazide, an erythematous pruritic eruption which contained scattered discrete purpuric spots that did not blanch on pressure developed on her lower legs. She had also been taking multivitamin tablets and Bufferin shortly prior to admission. Her past personal allergy history was negative, but the family history was suggestive of allergy. Laboratory findings on admission were essentially normal except for a lowered red cell count. The platelet count was normal, but there was a strongly positive Rumpel-Leede test.

When all medications were discontinued, the symptoms cleared quickly within 8 days, although the Rumpel-Leede test remained positive for a longer period of time. Patch tests with Lanoxin, Bufferin, and Diuril were negative, even with the application of negative pressure to the patch test. After all the lesions had cleared, resumption of chlorothiazide in a dosage of 0.5 gram twice a day produced exacerbation of the eruption within 24 hours. The lesions took 10 days to clear. R. W.

MISCELLANEOUS ALLERGIES

Blood Dyscrasias Associated With Antituberculosis and Combined Antituberculosis-Tranquilizing Chemotherapy. Worobec, T.: Dis. Chest **33**: 628, 1958.

After a month of treatment with para-aminosalicylic acid (PAS) and streptomycin (SM), a 31-year-old veteran with schizophrenia and pulmonary tuberculosis developed chills, fever, nausea, malaise, and a moderate pharyngeal inflammation. Tetracycline and penicillin were then included in the therapeutic regimen. Twelve days later the patient developed a generalized erythematous dermatitis, generalized lymphadenopathy, and a tender liver. SM and PAS were discontinued, and the temperature slowly subsided. Within a few days, however, he developed icterus as well as a white count of 25,000 with 80 per cent neutrophils, 18 per cent lymphocytes, and 2 per cent eosinophils. Liver function tests and urinalysis showed marked hepatocellular impairment. Within a few days his white count increased to 95,000 with 24 per cent neutrophils, 39 per cent lymphocytes, and 29 per cent eosinophils as well as 8 per cent monocytes, a blood picture resembling a leukemoid reaction with enlarged lymphocytes. The initial leukocytosis with 80 per cent neutrophils was considered to be a response to tissue damage. The subsequent lymphocytosis was regarded as a marked lymphoid or reticuloendothelial tissue response, and eosinophilia was compatible with an allergic state. Empirically, gamma globulin was given intramuscularly and there was a gradual improvement in his white count and liver function tests. Subsequently, a small test dose of streptomycin resulted in a reaction consisting of chills, fever, and skin rash. A test dose of Rezipas resulted in nausea, malaise, leukocytosis, and slightly abnormal liver function tests. Later, this patient was given INH and his tuberculosis was treated with surgery, resulting in marked improvement in his general condition.

The second patient, a 30-year-old white veteran with a psychiatric disorder and pulmonary tuberculosis, had been given streptomycin and INH in addition to 30 electroshock and 33 insulin shock treatments within a four-month period. Later, when this patient refused streptomycin injections, the regimen was changed to PAS and INH. He was placed on chlorpromazine, 50 mg. twice daily. Some months later he became an eating problem. He was therefore placed on supplemental tube feedings. A blood count at this point showed

6,800 white cells with 61 per cent neutrophils, 39 per cent lymphocytes, and 14 grams of hemoglobin. Three weeks later, after a supplemental feeding, he vomited. The next day he became acutely ill with chills and a temperature of 102.6° F., and his respirations were 28 per minute. The mouth and throat showed congestion but no ulceration. Suppressed breath sounds were heard over the lower half of the right lung, and after a few hours fine râles were heard and dullness was elicited on percussion. He developed a nonproductive cough, and a white count showed 1,250 white cells with 25 per cent neutrophils, 68 per cent lymphocytes, and 7 per cent monocytes. A diagnosis of granulocytopenia due to drug hypersensitivity and right lower lobe pneumonia was made. Chlorpromazine, PAS, and INH were discontinued and penicillin, tetracycline, and liver extract were administered. The patient's course continued downhill and he died with Cheyne-Stokes respirations and vascular collapse two days later. Necropsy revealed moderate fibrosis with an angiomatous pattern of congested blood vessels in the apex of the lung. Large areas of extravasated blood were also present. Other areas of the lung disclosed a pneumonia. Small fat droplets were seen in the liver cells, but there were no other findings to indicate toxic damage. There was moderate passive congestion of the spleen as well as the kidneys, and occasional minimal transudation in Bowman's capsules was noted. Bone marrow smears showed degeneration of myeloid cells while myeloblasts were aplastic.

In the first patient, with a leukemoid reaction, hepatitis, and dermatitis, it was thought that both streptomycin and PAS were injurious to the blood-forming organs. In the second case, with granulocytopenia and secondary confluent pleuropneumonia, all three drugs (chlorpromazine, PAS, and INH) were suspected, but it could not be determined which drug caused the irreversible damage to the bone marrow. E. W.

Components of Milk and Their Significance to the Allergic Child. Fries, J. H.: Ann. Allergy **17**: 1, 1959.

Allergic reactions to foods must be differentiated from reactions based on nonimmunologic mechanisms. Food intolerance may be the result of contamination with bacteria, insecticides, or antibiotics, overfeeding or underfeeding, or too rapid or forced feedings. In addition, there are a number of diseases induced by intrinsic factors in milk which are not immunologic in character. These include such conditions as breast milk intoxication due to vitamin B deficiency in the mother, the milk-alkali syndrome, macrocytic anemia due to prolonged feeding of goat's milk, and galactosemia.

The diagnosis of food allergy should be based on strict adherence to the criteria established for other allergic diseases and cannot be made simply on the basis of disappearance of symptoms with removal of the suspected food and the recurrence of symptoms with its reintroduction. At present the best approach to the problem of milk allergy is the substitution of evaporated or heated milk or one of the milk substitutes. Allergic sensitivity to milk is usually due to the lactalbumin fraction. Heat modifies this fraction sufficiently so that evaporated milk can usually be tolerated. If sensitivity exists to other protein fractions, however, it may be necessary to eliminate all milk and milk products as well as beef. If sensitivity to the heat-stabile casein fraction is present, a meat-base milk or soybean milk may be of benefit.

Vitamin deficiency, particularly a deficiency of vitamin A, may occur in the allergic patient as a result of dietary deficiencies or impaired absorption. In such cases supplemental vitamin feedings are indicated. H. F.

Acute Allergic Colitis Presenting the Clinical Picture of Acute Appendicitis. Karpman, H. L.: J. A. M. A. **169**: 1752, 1959.

A 47-year-old woman with a history of allergic rhinitis suffered cramplike lower abdominal pain and mild diarrhea shortly after the ingestion of lobster. Examination revealed right lower quadrant tenderness and a white blood count of 19,600. A diagnosis of acute appendicitis was made. At operation, part of the descending colon appeared to be thickened and edematous and there were numerous bullae along the mesenteric border. The bowel assumed its normal appearance promptly following the administration of 0.3 c.c. of 1:1,000 epinephrine, after which incidental appendectomy was performed. Pathologic examination of the appendix was negative. Skin tests performed with lobster extract postoperatively were negative.

The author states that even if the history and the favorable response of symptoms to epinephrine support a diagnosis of allergic colitis, it may nevertheless be prudent to operate when symptoms continue to suggest acute appendicitis or intussusception, since these conditions may coexist with allergic colitis. D. G.

Toxic Reaction to Intramuscular Injection of Iron. Shafer, W. A., and Marlow, A. A.: New England J. Med. **260**: 180, 1959.

A 46-year-old man with hypochromic microcytic anemia from bleeding hemorrhoids was given 200 mg. of iron-dextran intramuscularly for 4 days. Pain developed in several large joints and, when it subsided after several days, treatment was resumed. Again arthralgia occurred along with an area of cellulitis on one thigh. A scratch test with the iron-dextran combination was negative. A review of the literature indicated that incidence of reactions to this drug was low, but the following reactions have been reported: skin rashes, including 3 cases of urticaria and 1 of angioedema, 3 anaphylactoid reactions and generalized reactions, including 2 temperature elevations. M. C.

Allergic Reaction to Poliomyelitis Vaccine Probably Due to Penicillin. Pelner, L.: New England J. Med. **260**: 230, 1959.

A 28-year-old man received an injection of polio vaccine. The next day he noted slight stiffness of the neck, followed by malaise, fever, weakness, and generalized giant urticaria. He then developed swelling of the joints of the fingers and toes, and at the end of one week he became jaundiced. The liver edge was palpable two fingerbreadths below the costal margin, and the temperature ranged between 101 and 102° F. By the twelfth day lymphadenopathy was present, and exfoliation of the skin of the back, face, and toes occurred. On the fourteenth day, 800,000 units of penicillinase were given intramuscularly. The fever subsided the next day; the jaundice cleared and the urticaria did not recur. Approximately two and one-half months after the initial injection, the patient was given 1 c.c. of polio vaccine which had been reconstituted with polymyxin B instead of penicillin. No untoward reaction occurred. One year previously, the patient had experienced a serum sickness reaction to penicillin. For these reasons, penicillin was considered the most likely cause of the reaction. M. C.

A Case of Gangrene of the Foot in an Infant After Treatment With Penicillin. Kastel, K.: Harefuah **56**: 60, 1959.

A 3-month-old infant received three injections of procaine penicillin for bronchitis. Two days after the last injection, he developed a gangrenous lesion

of the left foot in spite of the fact that the posterior tibial and dorsal pedal arteries were palpable through the entire course of the disease. Bluish patches were noted on the left thigh, gluteus, and right foot. Blood could be displaced from these cyanotic areas by pressure, indicating that there was no thrombosis of the capillaries or venules. The gangrenous part of the left foot eventually dropped off, and the area was skin-grafted.

The author suggests that the gangrene was due to a vasculitis caused by an allergic reaction possibly to penicillin and/or procaine. I. G.

PHARMACOLOGY, PHYSIOLOGY, AND PATHOLOGY

Effect of Histamine and Histamine Liberator, Compound 48/80, on Blood Glucose. Papacostas, C. A., Mozden, P., and Loew, E. R.: Proc. Soc. Exper. Biol. & Med. **97**: 297, 1958.

Previous studies have provided evidence that small doses of histamine, injected intravenously, liberate epinephrine from the adrenal glands. A sensitive index of the presence of injected or liberated epinephrine is the hyperglycemia which results from the known glycogenolytic activity of this substance.

Following a fasting period, groups of unanesthetized male albino rabbits were injected with either 0.1, 0.15, or 0.2 mg. of histamine per kilogram of body weight in terms of base. Control animals received physiologic saline. Blood samples were collected at specified intervals before and after the injection. Four dogs were also injected on two separate occasions with saline and histamine. Similar studies were carried out in rabbits and dogs with compound 48/80, a potent histamine liberator. Blood glucose determinations were made by the semimicro technique of Folin-Malmros. In the rabbits, a graded hyperglycemia was demonstrated following histamine injection. Manifestations of shock were evident in many of the animals following 0.2 mg. histamine per kilogram, and in these cases a moderate hyperglycemia developed. In dogs, 0.2 mg. histamine per kilogram caused a significant increase in blood glucose, accompanied in each case by toxic symptoms. Lower doses elicited fewer symptoms but failed to raise the blood sugar. Since, in both species, small, nontoxic doses of histamine failed to induce significant hyperglycemic responses, it is likely that the epinephrine release and glycogenolysis which followed the injection of larger doses of histamine in dogs and rabbits results from reflex sympathetic activity coincident with shock.

In rabbits, even relatively high doses of compound 48/80 produced no significant changes in blood glucose, except for a slight hyperglycemia in two animals with mild manifestations of shock. In dogs, the lower doses of compound 48/80, although slightly toxic, had essentially no effect on blood sugar. However, a dose of 0.5 mg. per kilogram which resulted in severe symptoms, including prostration, produced a temporary hypoglycemia at a time when histamine shock would have caused a moderate elevation of blood glucose. The effects of compound 48/80 in the dog were not consistent with those following histamine shock, which suggests a hypoglycemic activity unrelated to the release of endogenous histamine. H. Stryker.

Increase in Circulating Red Cell Volume of Normal Rats After Treatment With Hydrocortisone or Corticosterone. Fisher, J. W.: Proc. Soc. Exper. Biol. & Med. **97**: 502, 1958.

Repeated injections of ACTH in normal mice and rats have been shown to cause an increase in hematocrit and total red cell volume. In this study,

groups of male albino rats were given daily subcutaneous injections of hydrocortisone acetate and corticosterone suspended in 0.9 per cent sodium chloride. Doses of 0.5, 2, and 5 mg. hydrocortisone per kilogram and of 5 and 10 mg. corticosterone per kilogram of body weight were administered for 60 to 90 days. Six untreated animals were studied as controls. Red cell counts, hematocrit, and hemoglobin determinations were made by standardized techniques. Blood volume studies were done, employing P^{32}-tagged erythrocytes injected into a thigh vein previously exposed under ether anesthesia. Mixed blood samples were removed for counting after the tagged cells had been allowed to circulate for ten minutes.

Hematocrit, erythrocyte, hemoglobin, and total cell volume values at 60 days were significantly elevated for all dosages of hydrocortisone and corticosterone. The most striking increases followed injections of hydrocortisone at 2 mg. per kilogram of body weight. The mean corpuscular volume was decreased after treatment, which explained the proportionately greater increase in red cell counts as compared with hemoglobin and hematocrit levels. The total circulating erythrocyte volume increased from 1.45 to 1.64 times that of the untreated controls. Mean corpuscular hemoglobin concentration remained essentially normal. These results suggest that the adrneal secretions play an important role in hematopoiesis. H. S.

Plasma 17-Hydroxycorticosteroid Concentrations in Fasted Dogs Following Oral Administration of Hydrocortisone Esters. Collins, E. J., Forist, A. A., and Nadolski, E. B.: Proc. Soc. Exper. Biol. & Med. **97**: 558, 1958.

The effect of esterification on the absorption and metabolism of hydrocortisone (F) and several F derivatives was studied in dogs. Trained dogs, each weighing 15 to 20 kg., were fasted for 16 to 18 hours prior to the oral administration of 20 or 40 mg. of F or an equivalent dose of various F esters. Blood samples were then obtained at hourly intervals for five hours. Food, but not water, was restricted during the sampling period. Plasma 17-hydroxycorticosteroid (17-OHCS) concentrations were determined by a special technique and recorded as a function of time following the oral administration of the steroids. The esters studied included hydroxycortisone cyclopentylpropionate (FCP), hydrocortisone acetate (FAC), hydrocortisone a-ethylbutyrate (FEB) and hydrocortisone a-ethylisovalerate (FIV). Only free 17-OHCS concentrations in the plasma were measured. Intact esters were not detectable in the samples, indicating that the free alcohol was the species metabolized.

Prompt elevation of 17-OHCS levels occurred within an hour following the oral intake of each of the esters. At the 20 mg. dose, the maximum concentrations were 45 to 73 per cent of the values observed after F, indicating a slower rate of absorption with the esters. The rate of removal of 17-OHCS following the administration of the esters was as rapid as that following the free alcohol administration. At the 40 mg. dose, the maximum concentrations were only 20 to 49 per cent of the level after F administration, but the apparent disappearance of the 17-OHCS from the blood stream was considerably retarded. This was probably a result of continuing absorption from the gastrointestinal tract. With the esters, the maximal absorption rate seemed to appear at a much lower dose level than with F itself. Increasing the dose did not greatly increase the maximum plasma 17-OHCS levels but maintained them at an elevated level for a longer period of time. Although many factors are concerned in the rate of steroid absorption, it may be concluded that the intestinal absorption of orally administered steroids is modified by esterification. H. S.

Studies on Platelets. XX. Further Characterization of the Electrophoretic Anomaly in Serum of Patients With Idiopathic Thrombocytopenic Purpura. Stefanini, M., and Moschides, E.: J. Lab. & Clin. Med. **51**: 842, 1958.

In electrophoretic experiments, the albumin fraction from normal human sera behaved as a single component when electrophoretically migrated in phthalate buffer and showed no appreciable stainable carbohydrate material. The albumin fraction from sera of patients with idiopathic thrombocytopenic purpura (I.T.P.) under identical experimental conditions separated into two components: a faster one (albumin-1) representing 24 to 36 per cent of all protein (70 to 85 per cent of the total albumin fraction) and a slower one (albumin-2) representing 3.5 to 11 per cent of all protein. The bound carbohydrate-protein ratio in terms of milligrams-to-grams approximated values of both 20 for albumin-1 and of 10 for albumin-2 fraction. Direct staining with a method of Köiw indicated that 75 to 80 per cent of all hexoses were found in albumin-1 and only 20 to 25 per cent in albumin-2. Similar results were obtained in sera of rabbits that had developed an auto- and iso-platelet antibody after stimulation with antigenically modified autologous platelets. In such sera, the albumin-1 contained 26 to 27 per cent of all protein and the albumin-2 contained between 14 and 17 per cent. The major differences between normal and I.T.P. sera resided in the total amount and in the distribution of hexoses and glucosamine in the various serum fractions. There was an appreciable increase of protein-bound hexoses as well as a significant rise of glucosamine in the sera of patients with I.T.P. No appreciable amount of hexoses or glucosamine could be detected in the eluate from the albumin fraction of normal sera, while the eluate from the sera of patients with I.T.P. contained 15 to 20 per cent of the total amount of protein-bound hexoses and approximately 30 per cent of the total glucosamine. The increase of total protein-bound hexoses and glucosamine in the sera of patients with I.T.P. appeared linked in their appearance in the albumin fraction, while their amount was essentially unchanged in the globulin fractions as compared to normal sera. It was suggested that these changes might indicate auto-immunization against platelets, especially since similar findings had been observed in the sera of rabbits which had developed auto- and iso-platelet antibodies after stimulation with autologous, antigenically modified platelets. E. W.

Adrenal Cortical Hormones and the Formation of Histamine and 5-Hydroxytryptamine. Hicks, R., and West, G. B.: Nature **181**: 1342, 1958.

Daily doses of cortisone or hydrocortisone (50 mg. per kilogram) were given for 14 days to groups of rats which were then killed. Several tissues were extracted and tested for histamine content and 5-hydroxytryptamine activity. The histamine levels in the skin of the treated groups fell to about 50 per cent of those in the skin of the control group. A similar loss of 5-hydroxytrpytamine also occurred. Degranulation of skin mast cells was particularly noticeable, but disruption of the cell membrane was absent. In the jejunum and spleen, only histamine depletion was detected. In sharp contrast, similar doses of desoxycorticosterone acetate failed to produce a decrease in tissue levels of either amine in any of the tissues studied and failed to alter the morphology of the mast cells. Similar experiments were conducted on rats treated with polymyxin B. This treatment depleted the tissues of histamine but failed to lower significantly the 5-hydroxytryptamine levels. Cortisone therapy in these rats retarded the recovery rate of tissue histamine, and the 5-hydroxytryptamine levels in the skin fell to about 20 per cent of the control values. On the other

hand, desoxycorticosterone acetate failed to alter the recovery rate of histamine or the tissue levels of 5-hydroxytryptamine.

It was suggested that cortisone and other glucocorticoids lower the activity of both histidine decarboxylase and 5-hydroxytryptophan decarboxylase, whereas desoxycorticosterone acetate and other mineral corticoids are devoid of this action. I. G.

The Demonstration of Tuberculin Hypersensitivity in Vitro. Marks, J.: J. Path. & Bact. **76**: 39, 1958.

Conflicting reports exist as to the lethal effects of tuberculin on tuberculin-sensitive cells in tissue culture. The original experiments were repeated, the original results in each case were confirmed, and certain problems of technique were found to account for the discrepancy in results. These are described in detail. It is still not possible to conduct quantitative studies of cell migration. However, it may be stated that, with optimal cultural conditions, tuberculin reduces the mobility of polymorphic neutrophils and macrophages in vitro without having a direct lethal effect on them. The glucose consumption of tuberculin-sensitized cells was not reduced by the addition of P.P.D. Phagocytosis and dehydrogenase activity of sensitized cells were only slightly affected by the addition of P.P.D. E. K.

The Pathological Changes Produced by Anti-Lung Serum. Read, J.: J. Path. & Bact. **76**: 403, 1958.

Rabbit anti-rat-lung serum was administered to rats intratracheally, intraperitoneally, or intravenously. Only the intratracheal route resulted in pulmonary changes characterized by a lobar type of pneumonia. The pathology was described in detail. Normal rabbit serum failed to elicit these lesions as did rabbit anti-rat-lung serum which was previously absorbed with rat lung suspension. The alveolar lining cells were considered to be the major target of the antibody reaction. E. K.

Aminophylline Poisoning. Report of a Case With Complete Pathologic and Toxicologic Findings. Couch, R. D., Franz, M., and Forney, R. B.: Am. J. Clin. Path. **30**: 435, 1958.

A 4-year-old child accidentally swallowed 17 enteric-coated tablets of aminophylline, 5 grains each, and from 6 to 12 capsules of Benadryl, 50 mg. each. Five or six partially dissolved aminophylline tablets were vomited from 1 to 2 hours after ingestion. His estimated total dose of aminophylline was 4.5 grams. He repeatedly vomited coffee-ground material, developed intermittent convulsions, coma, and dyspnea. He appeared to improve with oxygen and barbiturates but died abruptly 20 hours after ingestion of the tablets. Autopsy disclosed a greatly dilated stomach with multiple ulcerations; there was a perforation of the distal portion of the esophagus, and its mucosa was denuded. Hepatic cells were swollen and indistinct. The kidneys, brain, and adrenals were normal in appearance. Toxicologic analyses of the various organs for concentrations of aminophylline were presented. E. K.

The Effects of Aminophylline and Other Xanthines on the Pulmonary Circulation. Quimby, C. W., Jr., Aviado, D. M., Jr., and Schmidt, C. F.: J. Pharmacol. & Exper. Therap. **122**: 396, 1958.

Aminophylline is known to reduce pulmonary arterial blood pressure. Anesthetized dogs were studied by the pharmacologic procedures usually employed

in open chest preparations. Pulmonary outflow was measured directly from one lung lobe. The dogs were injected intravenously with aminophylline. It was found that this drug acted as a nonselective vasodilator, increasing both pulmonary and systemic blood flow. Myocardial contraction force was also increased to an extent which "favors the heart as the most important cause for increased pulmonary blood flow." Study of 40 other xanthines failed to disclose a selective pulmonary vasodilator. Bronchodilation was mentioned as another response to intravenous aminophylline. E. K.

IMMUNOLOGY

The Effect of Prednisolone on Circulating Antibody Formation in Animals Immunized With Human Platelet Antigen. Suhrland, L. G., Arquilla, E. R., and Weisberger, A. S.: J. Lab. & Clin. Med. **51**: 724, 1958.

Human platelet antigen obtained from six persons with normal platelets was conjugated to erythrocytes by the bis-diazo-benzidine technique. Nonconjugated platelet antigen and an adjuvant of falba and mineral oil were injected subcutaneously in eight different sites on the backs of rabbits. Half of the rabbits received 3.0 mg. of prednisolone daily by subcutaneous injection in two divided doses for six weeks. At the end of the fifth week all animals received a booster dose of pooled platelet antigen containing 5.0 mg. of protein. A second booster was given at the end of the seventh week. Blood was collected from the rabbits prior to the first administration of antigen and, except for the first week, at weekly intervals. The serum antiplatelet titer of the rabbits receiving prednisolone was compared with that of the untreated control animals. The presence of platelet antibodies was demonstrated by the hemagglutination of erythrocytes conjugated with antigen by rabbit antiplatelet sera. The antiplatelet rabbit serum was found to have a high degree of specificity for the agglutination of these erythrocytes. In control animals the antiserum titer rose gradually, and at the end of five weeks, following the initial injection of antigen, the titer ranged from 1:40 to 1:60. In contrast with this, the animals treated with prednisolone did not develop any detectable antibodies by the fourth week. When a booster injection was administered, the control animals showed a characteristic anamnestic response. Seven days following the booster injection, the antiplatelet titer of the controls was 1:160 to 1:640, whereas the antiplatelet titer of the prednisolone-treated animals was only 1:40 to 1:80. Prednisolone was then discontinued, and the antibody titers were determined after one week. At this point there was no demonstrable rise in the level of antibodies of soluble platelet antigen in either group of animals. A second booster injection was administered 14 days after the initial booster. Seven days later the control animals showed little change in circulating antibody, whereas all but one of the previously prednisolone-treated animals responded with a definite increase in antibody titers, which now ranged from 1:80 to 1:320. When massive doses of prednisolone, 30 mg. daily, were administered, there was almost complete inhibition of formation of detectable antibody to soluble antigen. When the drug was discontinued, however, the anamnestic response did not seem to be impaired in spite of previous massive amounts of prednisolone. Thus, while prednisolone inhibits the formation of antibody to platelets it does not prevent the production of a sensitized state. E. W.

A Skin Test in Thyroid Disease. Buchanan, W. W., Anderson, J. R., Goudie, R. B., and Gray, K. G.: Lancet **2**: 928, 1958.

The authors studied the possible autoimmunologic causes of thyroid disease. Skin tests were performed with a thyroid extract on 52 patients, of whom 33

had thyroid disease and 19 served as controls. The vast majority of patients of both the study and control groups were women, and all the control patients had a terminal illness but no clinical evidence of thyroid disease. The 33 patients with thyroid disease represented 11 cases of Hashimoto's disease, 8 of primary myxedema, 7 of thyrotoxicosis, 3 of simple nontoxic goiter, and 1 of thyroid carcinoma. Three patients also included in the group did not have a clear-cut diagnosis and were considered to have unclassified cases of thyroid disease. The solution used for skin testing was prepared from the surgically excised thyroid of a thyrotoxic patient. A sterile saline extract was prepared from the tissue, Seitz filtered, and then stored at −15° C. This antigen, in a 0.2 ml. volume, was injected intracutaneously on the volar aspect of the forearm. Some of the patients were also tested with a 0.2 ml. suspension of antigen to which a solution of cortisone acetate had been added or with a mixture of cortisone acetate combined with saline. Tests were read within 24 hours, when the maximal reaction was usually observed. Tests were not read as positive unless at least 1 cm. of erythema was present. A strongly positive test also contained a central area of induration. Fifteen of the patients with thyroid disease had positive agar diffusion precipitin tests to thyroid extract; 10 of these patients showed strongly positive skin tests, while 1 patient had a weakly positive reaction. Of the 37 patients with negative precipitin tests, 32 had negative skin tests and 5 had weakly positive skin reactions. Of the 5 persons with suggestively positive skin test reactions but negative precipitin tests, each at one time had questionable thyroid disease. The addition of cortisone to the thyroid antigen produced no consistent response but tended to enhance the skin reaction. In no instance did the intracutaneous injection of cortisone acetate and saline produce a positive skin reaction. The indurated lesions were very frequently painful and took 48 to 72 hours to subside. Biopsy of a positive skin reaction showed extensive edema with hemorrhage into the dermis and subcutaneous tissues. There was a marked infiltration of polymorphic neutrophils, many of which were necrotic, and some eosinophils. Since the strongly positive skin reactions were observed only in patients with thyroid disease who concomitantly had precipitating thryoid antibody in their serum, thyroid antigen appears capable of producing an abnormal tissue reaction in certain patients with thyroid disease of possible autoimmune etiology. R. W.

Thyroid Antibodies in Myxoedema. Owen, S. G., and Smart, G. A.: Lancet **2**: 1034, 1958.

The sera of 78 patients with spontaneous nongoitrous myxoedema and 77 patients with Hashimoto's thyroiditis were studied for the presence of thyroid antibodies. Fifty-two hospital patients without evidence of thyroid disease were employed as controls. The level of circulating antibodies to thyroid protein was estimated by a precipitin technique which utilizes the tannic-acid hemagglutination method. Tanned red cells coated with thyroid antigen from a thyrotoxic person were exposed to serial dilutions of sera obtained from the various patients, and the amount of circulating antibodies was measured. The number of patients with myxoedema was approximately equal to the number with Hashimoto's disease who demonstrated circulating antibody to thyroid protein, although patients with acute Hashimoto's disease showed much higher titers. Thyroid therapy did not influence the titer of patients with myxoedema, but in Hashimoto's disease treatment for more than a year tended to be associated with titers approximating those characteristic of myxoedema. Only 3 controls, all of whom were female, showed positive antibody titers. It is suggested that a similar mechanism is responsible for the etiology of both myxoedema and Hashimoto's disease. R. W.

Studies in Human Sensitivity to Antibiotics. I. Testing for Precipitins After Reaction to Antibiotics. Muelling, R. J., Jr., Beven, T., Samson, R. F., Jenevein, E. P., and Guillory, J. D.: Am. J. Clin. Path. **29**: 503, 1958.

By means of a gel diffusion technique, precipitins were demonstrated in sera taken from patients suspected of having allergic reactions to an antibiotic. An observation period of from 5 to 21 days was required to read the diffusion tubes. It was felt that the precipitin reaction was useful in "proving" or disproving the allergic nature of the clinical picture observed. Precipitins were observed in one case 4 years after a penicillin reaction and were absent in another case 5 years after a penicillin reaction. The latter patient was treated with penicillin without incident. Precipitins were also observed to streptomycin, novobiocin, oxytetracycline, erythromycin, chloramphenicol, oleandomycin, and tetracycline. E. K.

The Metabolism of Some Antigen-Antibody Complexes in the Rabbit. Walter, H., and Zipper, H.: J. Immunol. **82**: 12, 1959.

Rabbits sensitized to beef gamma globulin (BGG) and normal animals received injections of I^{131}-BGG–anti-BGG complex in the marginal vein of the ear. Studies over a period of 7 days were made on the protein-bound radioactivity in the blood and organs of these animals. The report of other workers that blood clearance proceeds more rapidly in sensitized than in control animals was confirmed. The presence of excess antibody in the sensitive animals reduces dissociation of the antigen-antibody complex in the blood so that it is more rapidly eliminated. Immediately after injection of the complexes, the lungs show the highest specific and total activity in localizing the antigen in both the sensitive and control animals. Later the spleen and lymph nodes show the highest specific activity among the organs, although the liver and lungs, because they are so large, are responsible for the greatest removal of injected activity. The spleen is more active in the sensitive than in the control animals, but the general organ distribution pattern is the same in both series of animals.

The authors' findings are in agreement with those of Dixon and Talmage, who studied the problem in actively and passively sensitized animals. They interpret their results to indicate that the elimination of antigen-antibody complex does not depend on tissue sensitization. "The mechanism of antigen-antibody complex removal seems essentially to be one either of filtration by the reticuloendothelial organs or of entrapment as emboli." B. S.

Sensitivity of Pertussis-Inoculated Mice to Endotoxin. Kind, L. S.: J. Immunol. **82**: 32, 1959.

In the pertussis-inoculated mouse, sensitivity to endotoxin is correlated with the development of susceptibility to histamine and serotonin. *B. pertussis* and other gram-negative organisms alter the susceptibility of mice to bacterial infections, making them more susceptible to some and more resistant to others. Whether pertussis inoculation causes an increase or decrease of susceptibility to bacterial infection will depend on a variety of factors, such as the dose of pertussis vaccine administered and the nature, virulence, and route of inoculation of the infecting organism.

Thirteen days after pertussis inoculation, mice show an increase in susceptibility to *E. coli* endotoxin or organism. This susceptibility may be reversed by preliminary injections of small, sublethal doses of *E. coli* endotoxins. This reversal does not modify the increased susceptibility of these animals to histamine or anaphylactic shock. In fact, pretreatment with *E. coli* endotoxin may

actually increase the degree of anaphylactic sensitivity in the pertussis-treated mouse while it may at the same time increase the resistance of these animals to subsequent injections of pertussis vaccine. Nonspecific factors are important in some of these phenomena, and the author warns against interpreting some instances of apparent bacterial allergy solely in terms of antigen-antibody systems. B. S.

Studies on the Transfer of Lymph Node Cells. XIII. Effect of X-irradiation on Lymph Node Cells Incubated In Vitro With Shigella-trypsin Filtrate. Harris, T. N., Harris, S., and Tulsky, E.: J. Immunol. **82**: 26, 1959.

Cells were obtained from lymph nodes of normal donor rabbits or from animals previously injected in their foot pads with a heterologous antigen (sheep erythrocytes). The donors were sacrificed four days later and the cells were teased from the lymph nodes and incubated with antigen. The effects of irradiation on antibody production were studied in three ways: (1) when the recipient animals were irradiated after transfer of incubated lymph node cells, (2) when donor lymph node cells were irradiated in vitro, before they were transferred to irradiated recipients, and (3) when donor rabbits were irradiated 24 hours before providing cells. The transfer of cells irradiated at dosages between 150 r and 400 r resulted in reduced agglutinin titers in the recipients. Such effects were found when the cell irradiation took place in the tissues of the donor, in the recipient animals, or in vitro. With increasing dosages of irradiation, there was a steady decline in the agglutinin titers and this occurred in the case of cells irradiated in vitro or in the tissue of the donor or of recipient rabbits.

The transfer of irradiated lymph node cells to normal recipients did not result in the production of more antibody than that which occurred after the transfer of such cells to irradiated animals. T. CHAO

The Precipitin Reaction Between DNA and a Serum Factor in Systemic Lupus Erythematosus. Deicher, H. R. G., Holman, H. R., and Kunkel, H. G.: J. Exper. Med. **109**: 97, 1959.

Sera from 8 of 14 patients with acute systemic lupus erythematosus (SLE) gave precipitin bands in tubes layered with serum, agar, and highly purified desoxyribonucleic acid (DNA). All 6 patients who failed to show this reaction had positive LE cell tests. Other sera, however, including those of normal persons and patients with acute rheumatic fever, rheumatoid arthritis, cirrhosis of the liver, chronic hepatitis with hypergammaglobulinemia, or advanced scleroderma, failed to show precipitin reactions with DNA. Solutions of human gamma globulin also failed to react with DNA. Treatment of the DNA solution with its destructive enzyme abolished the precipitin band. The reaction occurred with DNA obtained from many sources, including calf thymus, salmon sperm, and human liver or leukocytes. Characteristic precipitin curves were obtained in titrations of 3 positive sera with DNA, with zones of antibody excess, equivalence, and antigen excess. Complement was fixed in the reaction. "As the precipitin curve approaches the equivalence zone, the complement fixation titre against DNA decreases and disappears near the equivalence point while the complement fixation titre against nucleoprotein is only partially removed, indicating the presence of more than one factor reacting with nucleoprotein." Precipitates of serum factor and DNA were partially dissociated with DNAase and the protein removed gave reactions of identity with fraction II gamma

globulin by immunologic tests and on electrophoresis. A more rapid mobility of this protein in agar than in gamma globulin was found but has not been explained.

All sera continued to show LE cell formation even when DNA precipitates had been removed at the equivalence point or in the region of DNA excess. Eluates of the DNA precipitates did not induce the formation of LE cells. It is now suggested that the DNA precipitating factor and the LE cell inducing factors are separate gamma globulins which may be separated and need not coexist in this disease.

It is concluded that the precipitating factor probably represents an antibody to DNA and that it is one of a number of autoantibodies elicited in this disease. E. K.

MISCELLANEOUS

Pulmonary Aspergillosis With Cavitation: Iodide Therapy Associated With an Unusual Electrolyte Disturbance. Utz, J. P., German, J. L., Louria, D. B., Emmons, C. W., and Bartter, F. C.: New England J. Med. **260**: 264, 1959.

Two patients with marked cavitation and abscess formation in previously damaged lungs (carcinoma in one and pulmonary fibrosis in the second) were found to be infected with *Aspergillus niger*. The first patient received 30 Gm. of potassium iodide daily for two and one-half weeks, and the second was given 24 Gm. daily for three and one-half weeks. The fungus disappeared from the sputum and cavity material following this therapy. With the exception of nausea and a metallic taste in the second patient neither patient had any of the usual manifestations of iodism. Abnormalities were observed in the serum electrolytes. Hypokalemia, hyponatremia, and elevation of the CO_2 content occurred in both patients, and one also showed hypocalcemia and hypophosphatemia. M. C.